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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,682	04/28/2000	DAVID J. FITZGERALD	015280-31010	5396

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EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,682	FITZGERALD, DAVID J.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-8,11-23,26,28,31,32,34-36 and 39-43* is/are pending in the application.

4a) Of the above claim(s) *4-6,11,14-23,26,28,31,32,34-36 and 39-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,7-8,12-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim 1 has been amended.

Claims 9-10,24-25, 27, 29, 30, 33, 37-38, 44-45 have been canceled.

Claims 4-6, 11, 14-15, 16-18 (claims 16-18 recite specific species of invention not elected), 19-23, 26 (species not elected), 28, 31, 32, 34-36, 39 and 40-43 are withdrawn from further consideration as drawn to non-elected inventions.

Claims 1-3, 7-8, 12-13 are under consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 24, 2003, has been entered.

Rejections Withdrawn

rejected

3. Claim 8 under 35 U.S.C. 112, second paragraph is asserted to be clear in light of the definition provided in the specification, in light of the definition provided in the instant specification for PE domain II.

4. Claims 1-3,7-9, 12-13, 24-25 and 44-45 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, in light of the amendment of claim 1 to recite the loop to be in PE domain Ib, and the cancellation of claims.

5. Claims 1-3, 7-9, 11-12, 24-25 and 44-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the amendment of claim 1 to clarify the two cysteine residues and the cancellation of claims.

6. Claims 24-25 of this application conflict with claims 1-7, 20-24 and 32-38

of Application No. 09/462,713. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application, in light of the cancellation of claims 24-25.

Claim Rejections - 35 U.S.C. § 112

7. Claims 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 recites the combination of claim limitations "a translocation domain comprising an amino acid sequence at least 60% identical to a sequence of PE domain II. Domain II comprises amino acids 253-364 of Pseudomonas aeruginosa exotoxin A, but all of the amino acids of domain II do not enable translocation. As the amino acid sequence of section (2) may be any sequence that corresponds to any portion of an amino acid sequence of domain II, and need not be identical to the amino acid sequence of domain II but is claimed to be "at least 60% identical" to an amino acid sequence of domain II (this ~~phase~~ phrase include fragments and portions of any amino acid sequence for domain II), the instantly claimed invention is not enabled for the utilization of any sequence that shares "at least 60%" identity with any size or sequence of domain II, as all sequence contained in domain II do not have translocation activity, specifically amino acids 253-279. The instant specification has not described the genus of translocation domains that only share 60% identity with domain II, through the description of the species amino acid sequences of amino acids 253-364 and 280-364 of Pseudomonas exotoxin A. The claimed amino acid sequence is not required to comprise any critical amino acid sequence that would enable translocation of the chimeric immunogen across a membrane into a cell cytosol. Even if the claim were amended to recite 100% sequence identity to an amino acid sequence of domain II, absent

the amino acid sequence comprising a critical amino acid sequence that would evidence translocation activity, the instantly claimed invention is not enabled for the claimed invention.

8. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term: ("PE-like"); what is intended by a term in brackets and in quotes is unclear.

Claim 1 recites the phrase "capable of effecting translocation to a cell cytosol". When is the sequence that is 60% identical to a sequence of PE domain II capable of effecting translocation? What type of cell is the sequence capable of effecting translocation in? Does the translocation domain have the recited capability or is it just capable of effecting translocation when in association with additional sequences? What the capability is or what defines the capability is not distinctly claimed.

Claim 1 recites no specific size sequence of any specific amino acid sequence which the PE domain II must be 60% identical to. The invention is not distinctly claimed as it is unclear what the translocation domain sequence is, in light of the fact that domain II comprises a sequence of PE domain II, but this sequence only shares 60% sequence identity with the sequence of domain II of PE, and the sequence of PE in Swiss-Prot shows PE to evidence amino acid variance at

several locations. The claimed invention is not being defined by any specific sequence. What is the inventive domain II?

Claim 1 recites the phrase "an epitope presenting domain located at the PE Ib domain location"; this phrase lacks antecedent basis in the claim as no specific locations or arrangements of the domains have been required. Where is the location in light of the fact that the immunogen is not required to be constructed in a specific order based upon the recitation of the term "comprising" on line two of the claim?

Claim 1 recites the phrase "non-toxic Pseudomonas exotoxin A like chimeric immunogen; the immunogen comprises:

1) a cell recognition domain from **any source**;

2) a translocation domain that only share 60% identity to an amino acid sequence of PE domain II and therefore could be from **another source**;

3) an ER retention sequence **from any source**; and

4) a heterologous sequence in the PE Ib location of PE. What portion of the claimed immunogen is like PE? The cell recognition domain is not from PE, the ER domain is not required to be from PE, the epitope is "non-native" to PE and the translocation domain is only 60% identical to an amino acid sequence of PE and is not required to be PE. Three of the four domains are not from PE and the forth domain is not identical to that of PE but only shares a portion of a sequence that is 60% identical to PE, the size and sequence that is

similar is not distinctly claimed. How is the claimed chimeric immunogenic like PE in light of the fact that no single domain is required to be from PE?

Claim Rejections - 35 U.S.C. § 102

9. Claims 1,3, 7-8,12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Murphy (filing date June 7, 1995, US Pat. 6,022,950).

Murphy disclose the instantly claimed invention directed to a non-toxic (see col. 7, lines 9-11), Pseudomonas exotoxin A-like chimeric immunogen, wherein the chimeric immunogen comprises:

a. A cell recognition domain (see col.2, lines 61-64; claims 1-2, 14, includes Pseudomonas exotoxin A);

b. A translocation domain which shares at least a single amino acid in common with PE domain II and shares a common biological function for translocation (see col. 2, lines 65-67 and col. 3, lines 17-36, especially lines 19-20; col. 18, claim 1, paragraph (b));

c. A heterologous epitope (third part antigen) is located following the cell recognition domain and the translocation domain in an cysteine/cysteine disulfide loop (see col. 19, claims 21, 22, 43, claim 4), and before the endoplasmic reticulum domain (see claim 26, wherein at least cholera toxin, LT toxin and Pseudomonas aeruginosa exotoxin A comprise a heterologous epitope to the cell binding domain and the translocation domain, which is prior to the occupance of the endoplasmic reticulum retention sequence which is located at the C-terminal of the toxin).

d. An endoplasmic reticulum retention domain(see col. 19, claim 26; among the toxins recited in claim 26, endoplasmic reticulum retention sequences are inherent therein (KDEL or REDLK) comprises a heterologous epitope and an endoplasmic retentions sequence. Murphy inherently anticipates the instantly claimed invention.

10. Claims 1,7-8, 12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Pastan et al (effective filing date October 15, 1995, US Pat. 6,074,644, different inventive entity).

Pastan et al disclose the instantly claimed invention directed to a non-toxic Pseudomonas exotoxin A-like chimeric immunogen (see col. 4, lines 31-32 "cytotoxic activity substantially eliminated), wherein the chimeric immunogen comprises:

a. A cell recognition domain (Fv fragment which is also the epitope presenting domain located at the PE Ib domain location (see Figures 1 (B1(dsFv)PE33 and 5 (B3(VH)-P33-VL, disulfide-stabilized (ds) target-binding agent variable region of an antibody molecule; col. 6, lines 9-16);

b. A translocation domain shares at least a single amino acid in common with PE domain II and shares a common biological function for translocation (see PE domain II, see col. 6, line 26, and Figures);

c. An endoplasmic reticulum retention domain (see Pseudomonas exotoxin A endoplasmic reticulum retention sequences are inherent therein (KDEL or REDLK), see col. 6, lines 27-28, and Figures 1 and 5)

d. A heterologous epitope is located in Ib position of the Pseudomonas exotoxin A-like chimera (see col. 26, lines 13-24), wherein the heterologous epitope is positioned between a cysteine/cysteine disulfide loop (see Col. 6, lines 66-67 and col. 7, lines 1-6) and before the endoplasmic reticulum retention domain. Pastan et al anticipates the instantly claimed invention.

11. Claims 1, 3, 7, 8, 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Pastan et al (filing date January 8, 1997, US Pat. 6,011,002, different inventive entity).

Pastan et al disclose the instantly claimed invention directed to a non-toxic (decreased nonspecific cytotoxicity toward cells without affinity for the cell recognition domain, see col. 17, lines 44-45; the chimeric immunogen is non-toxic to non-selected cells) Pseudomonas exotoxin A-like chimeric immunogen (see col. 16, line 7), wherein the chimeric immunogen comprises:

a. A cell recognition domain (col. 5, lines 39-46; and also includes domain Ia; col. 15, line 61);

b. A translocation domain which shares at least a single amino acid in common with PE domain II and shares a common biological function for translocation (see PE domain II, see col. 15,lines 62-63);

c. An endoplasmic reticulum retention domain (see col. 16, lines 22-37)

d. A heterologous epitope is located in Ib position of the Pseudomonas exotoxin A-like chimera (see col. 17, lines 21-24), wherein the heterologous epitope in positioned between a

cysteine/cysteine disulfide loop (see col. 5, lines 66-67 and col. 9, lines 1-6) and before the endoplasmic reticulum retention domain (see col. 18, lines 20-26). Pastan et al inherently anticipates the instantly claimed invention (see all claims).

Claim Rejections - 35 U.S.C. § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-3, 7-8, 12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Wels et al (filing date April 25, 1997, US Pat.6,498,233) in view of Pastan et al (effective filing date October 15, 1995, US Pat. 6,074,644, different inventive entity).

Wels et al teach and show the formulation of a non-toxic (see col. 7, lines 49-52) Pseudomonas exotoxin A-like chimeric immunogen, wherein the chimeric immunogen comprises:

a. A cell recognition domain (see col. 97, claim 1; col. 5, lines 23-67, col. 6 and col. 7, lines 7-32);

b. A translocation domain which shares at least a single amino acid in common with PE domain II and shares a common biological function for translocation (see col. 97, claim 1; col. 7, line 47);

c. An endoplasmic reticulum retention domain(see claim 3, col. 98, line 59; col.8,lines 15-25); and

d. A heterologous epitope which is a nucleic acid binding domain that is in the location of the Ib domain, the location being one which follows the cell recognition domain and the translocation domain, and before the endoplasmic reticulum domain (see col. 97, claim 1; col. 7,

lines 60-67 and col. 8, lines 1-14), wherein the chimeric immunogen has functional domains like that of Pseudomonas aeruginosa exotoxin A (see col. 4, lines 26-30), and therefore is a Pseudomonas aeruginosa exotoxin A like protein. Wels et al shows the heterologous epitope domain to be located in the Ib position that is a nucleic acid binding protein domain (see claim 1 of Wels et al), but differs from the instantly claimed invention by failing to show the heterologous epitope domain to be contained in a cysteine-cysteine loop at the Ib location.

See discussion of Pastan et al above. Pastan et al teach a non-toxic Pseudomonas exotoxin A-like chimeric immunogen (see col. 4, lines 31-32 "cytotoxic activity substantially eliminated), which comprises a cell recognition domain, a translocation domain which shares at least a single amino acid in common with PE domain II, an endoplasmic reticulum retention domain ((KDEL or REDLK) and an heterologous epitope is located in Ib position of the Pseudomonas exotoxin A-like chimera (see col. 26, lines 13-24), wherein the heterologous epitope in positioned between a cysteine/cysteine disulfide loop (see Col. 6, lines 66-67 and col. 7, lines 1-6) and before the endoplasmic reticulum retention domain in an analogous art for the purpose of producing a chimeric Pseudomonas exotoxin that comprises a "disulfide stabilized binding agent".

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the Pseudomonas exotoxin-like chimeric immunogen of Wels et al with the cysteine-cysteine loop of Pastan et al because both Wels et al and Pastan et al insert heterologous epitope containing polypeptides into the Ib domain of the Pseudomonas exotoxin-like chimera and Pastan et al provides motivation to modify the Ib domain location that comprises

a heterologous epitope to include a stabilizing confirmation introduced through a cysteine-cysteine disulfide bond, which results in a disulfide stabilized binding agent, a domain that comprises a heterologous epitope that is stabilized.

The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a stabilized chimeric Pseudomonas exotoxin immunogen that comprises a stabilized Ib heterologous epitope because, Wels et al utilizes Pseudomonas exotoxin A in the production of a chimeric molecule with modifications in the Ib domain, and Pastan et al teaches and provides guidance for the modification of Pseudomonas exotoxin A Ib domain which results in a chimeric molecule with greater stability therein.

In the absence of a showing of unexpected results, Wels et al in view of Pastan et al obviates the instantly claimed invention.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
15. Boyd et al (US Pat. 5,843,882) is cited to show a conjugate that comprises and effector molecule that binds to HIV glycoprotein gp120, and Pseudomonas exotoxin.
16. Ladant et al (US Pat. 5,935,580) is cited to show a chimeric toxin of Bordetella which comprises a loop epitope presenting domain (see col. 3, lines 65-67, col. 4, lines 1-4), a cell binding domain and a translocation domain (see col. 6, line 1 and lines 5-26).
17. Murphy (US Pat. 5,965,406) is cited to show Pseudomonas aeruginosa like chimeric immunogens (see title, abstract, col. 2, line 45).
18. Pastan et al (US Pat. 5,980,895) is cited to show Pseudomonas exotoxin A-like chimeric immunogens that have epitope carrying disulfide loops in the Ib location (see all claims).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner

can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
August 23, 2002

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